The Honorable Gus Bilirakis

1. One mechanism drug companies have to improve certainty about the Agency's acceptance of certain trial designs is to enter into a Special Protocol Assessment (SPA) agreement, which was first authorized in 2007 for that very purpose. Have these agreements generally brought the intended certainty to companies and has the Agency always held up its end of the binding contract?

   Answer. PDUFA specifies three categories of eligibility for special protocol assessment: 1) animal carcinogenicity protocols, 2) final product stability protocols, 3) clinical protocols for phase 3 trials whose data will form the primary basis for an efficacy claim. The protocol is most often used by small companies who are seeking more certainty and who may not have the resources or time to withstand the need for additional studies. An SPA is generally binding upon the FDA unless a substantial scientific issue essential to determining safety or efficacy is identified after the testing begins. It therefore cannot and should not be viewed as a "contract" with FDA guaranteeing approval if the endpoints in trials are met. I believe in most cases the agency has honored the agreement, but I have not been able to obtain data to date. Furthermore, I am aware that there have been several high visibility cases where FDA has required additional studies despite an SPA agreement. I have not used the SPA process personally - instead preferring to work with FDA throughout the development process and to develop a program based on their input at end of phase II. This has generally succeeded when the data support the intended use. I do think that clarity of message and communication is critical and can be improved. Some Divisions of FDA seem to provide better clarity than others. I believe that FDA should strive for consistency across its Divisions to the extent possible and be resourced to provide more meeting time with sponsors for clarification. Perhaps a formal survey of sponsor satisfaction on the process after an action is taken would be useful for the Agency and Congress.

2. For Accelerated Approvals to work, the FDA needs to be comfortable using surrogate end points That is reasonably likely to predict a clinical benefit. The Report to the President talks about how the biomedical research community should take a more active role in determining endpoints. How can FDA work with stakeholders to determine endpoints that are reasonably likely to predict a clinical endpoint? Has the FDA been receptive to working with stakeholder on this?

   Answer: This is a very significant issue because lacking acceptable endpoints repels investment in many serious diseases. FDA has been (understandably) reluctant to accept non-validated surrogate endpoints presented by individual sponsors for use with specific therapies. This is usually because of a lack of data that would support generalizability as well to accurately predict a real clinical benefit. Individual sponsors have a very difficult time overcoming this – as well as issues of time and cost. However, there is an opportunity for public private partnerships that include NIH and FDA as well as patient advocates and industry to address this. The Biomarker Consortium[1] (managed by the Foundation for the NIH) is one such partnership that I have been involved with since its inception in 2006. It is a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health that endeavors to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics. Founding members include the NIH, FDA, CMS, BIO, PhRMA and several pharmaceutical companies. A number of important studies have been conducted and are underway.

[1] https://www.biomarkersconsortium.org

Additional efforts need to be undertaken. I believe that in many cases it would be possible to develop provisional surrogate markers based on consensus of leading academics, patient advocacy groups and the FDA. Such markers could be used to develop new therapies now, with additional evidence developed with longer-term follow-up. Some of these markers will thus be validated whereas others may be shown to be less reliable of definitive outcomes, resulting in label changes as appropriate, or in some cases even product withdrawal. Such provisional markers could be proposed by consensus conferences under a public private convening organization such as the Regan-Udall Foundation and could be further assessed by FDA advisory committees if needed. I would urge Congress to commission further study of this topic and to assist in any way possible to expedite implementation of strategies to accelerate surrogate and clinical endpoint development.

3. What barriers are currently in place that limit the potential of using clinical and outcomes data to learn more about how therapies are working on patients in the real world? How should we address them?

Answer: Real world data, that is data that are collected outside clinical trials, are abundant and contain a wealth of information. Unfortunately, these data remain difficult to efficiently access and analyze. A major problem with most observational data is an inherent inability to correct for unmeasured confounders and biases. Nevertheless, such data are very useful to monitor costs and quality, to assess use patterns of physicians and to generate hypotheses for further testing. Widespread use of electronic health records (EHR) will substantially increase the availability of richer clinical data sets. However, EHRs are designed to meet clinical practice needs. Successful use of EHR for clinical research requires that a number challenges be overcome. These include the need to integrate information technology (IT) systems, reconciliation of different terminologies and managing numerous regulatory and institutional requirements that do not support EHR use for clinical research[2]. Mandating data and regulatory standards for EHR including the ability to use de-identified data in limited ways as part of the consent for treatment at every clinic and facility would help to facilitate such studies.

Randomized trials are expensive and have been criticized as lacking applicability to clinical practice[3]. However, at present confounding and bias can only be effectively managed by randomization. New randomized trial designs have recently emerged that address these issues. Pragmatic trials are conducted in real-life settings encompassing the full spectrum of the population to which an intervention will be applied[4]. As long as patients are selected for a given therapy randomly to avoid selection bias by the physician data derived from such studies may have value for patients, practitioners, policy makers and the biopharmaceutical and medical device industries alike. As I mentioned in my previous written testimony one of the most interesting experiments currently underway is the NIH Collaboratory project[5].

On their website, Collaboratory describe themselves as follows: "Supported by the Common Fund at the National Institutes of Health, the Health Care Systems Research Collaboratory is intended to improve the way clinical trials are conducted by creating a new infrastructure for collaborative

research. The ultimate goal is to ensure that healthcare providers and patients can make decisions

[2] http://www.clinicalresearchforum.org/EHR4-4-14_white_paper_draft.pdf
[3] Why are so few randomized trials useful, and what can we do about it? Zwarenstein M, Oxman A, Pragmatic Trials in Health Care Systems (PRACTIHC). *J Clin Epidemiol.* 2006 Nov; 59(11):1125-6.
[4] A pragmatic view on pragmatic trials. Patsopolous, N. *Dialogues Clin Neurosci*. Jun 2011; 13(2): 217–224.
[5] http://www.nihcollaboratory.org

based on the best available clinical evidence. The NIH HCS Research Collaboratory also supports the design and rapid execution of several high-impact Pragmatic Clinical Trial Demonstration Projects that will address questions of major public health importance that engage health care delivery systems in research partnership." The group is led by outstanding clinical investigators and merits close observation. More such efforts should be encouraged by Congress.

However, in addition we should also strengthen and improve our conventional randomized control trial infrastructure by encouraging more patients to enroll, facilitating creation of standing clinical trials working groups and examining ways to reduce the cost of monitoring based on need and risk.

4. Once a drug is on the market, PCAST asserts that the economic incentives for drug companies to conduct further clinical trials to obtain formal approval for additional indications may be low. The report also points to the many difficulties of enrolling patients in clinical trials after the drug is already on the market. That being said, data about how the drug is working on patients in the real world is not confined to the indications approved for marketing. How can this real world data be leveraged for supplemental applications?

   Answer: I respectfully disagree with that assertion by PCAST. Formal approval is more important than ever for compliance purposes, especially given recent aggressive enforcement. Additional research investment to expand the indications or dosing regimens for an approved product is usually very lucrative for a manufacturer. Such studies are usually lower risk than pursuing new molecules, and also expand the safety database. In my experience, it has not proven difficult to find patients for new studies of drugs that offer real benefit, address areas or real need and answer questions of real importance to the ecosystem. That said, the efficiencies of trial execution in general should be greatly improved to lower costs and shorten timelines for the benefit of the entire ecosystem.

   When patient populations are small and diseases are very serious and/or life threatening (such as rare and orphan diseases, certain cancers), most patients will understandably not want to be randomized to placebo or less effective therapies. In these cases, trial designs that compare multidrug regimens, higher or lower doses, new dosing regimens are feasible in my experience and allow valuable new information to be gained, new populations to be studied and the safety database to be expanded.

   Sponsors have also been criticized of "dragging their feet" on performing post approval commitment studies. In my experience, this is not the case, although FDA has sometimes requested studies that are difficult to perform due to lack of patients. Sponsors sometimes agree to perform such studies in order to gain approval without carefully analyzing the feasibility of the trial. Once again building a more robust clinical trials infrastructure including better means of identifying patients and the ability to perform "pragmatic trials"[6] should help. However, FDA now has broad enforcement power in this regard and compliance should not be an issue.

   I believe that real world (observational data) are very valuable and a number of policy issues to facilitate use of such data such as ensuring that patients consent to the use of their de-identified data in limited clinical research without the need for individual consent and IRB review. However, one can easily be misled by such observational data owing to the potential for selection bias by physicians, e.g., a new drug may appear to be associated with a higher incidence of side effects

[6] A pragmatic view on pragmatic trials. Patsopolous, N. Dialogues Clin Neurosci. Jun 2011; 13(2): 217–224.

than an older drug when the opposite is true because 1) the older drug may be less scrutinized, 2) the physician may select the new drug for her sicker patients believing it to be better with different outcomes. For these reasons we should continue to invest in pragmatic trials that allow randomization such as those currently being piloted in the Collaboratory[4].

5. As a Member of Congress, we hear tales about how companies meet with FDA on drug approval and about their frustration with the process sometimes. Reviewers change during the approval process or may lack expertise about the latest science in a given area. How can FDA work with stakeholders to ensure that their management and review team is knowledgeable about the latest science?

Answer: As I noted in my answer to Rep. Schakowsky, I have interacted with FDA for more than 20 years. The large majority of FDA scientists are among the most dedicated civil servants one could ever encounter. Among them are former academics and industry scientists who moved to FDA to help advance innovation and to improve the public health. Some are among the world's best clinical scientists – even though they may not always be recognized as such. However, like every large organization, there are underperformers, although they are in the minority. It sometimes seems that senior FDA leadership do not currently have the tools needed to manage performance optimally. Thus consistency can suffer.

PDUFA has certainly improved the productivity of the agency and provided more rigorous timelines for review. However this has come at a price. FDA workload has outpaced their budget and staff. The intramural research program of FDA has been greatly reduced. FDA scientists have serious travel restrictions that do not allow them to attend scientific conferences as frequently as they should and to have meetings with leading academics. Thus the culture of the FDA has become increasingly "bureaucratized" and less scientific. One can contrast this culture with that of the NIH. Given the complexity of the new products in the pipeline including stem cell and gene therapy, smart devices and so on this does not bode for our competitive position in the world.

A number of the most senior and best scientists have or will soon retire. They will be difficult to replace. An increase in the budget for intramural science would attract higher quality scientists and raise their visibility in the academic community. The emphasis should be placed on clinical trials, regulatory science, toxicology, and other scientific disciplines directly related to the FDA mission. Increased budget for attendance at scientific conferences and training would also help. Top scientists should be recruited. Excellent performers should be rewarded and poor performance should be managed. Information management technology needs to be upgraded. Processes need to be improved so that busy work is reduced in favor of value added activities. We need to maintain a world class, science driven FDA. In my view, such reforms would greatly improve the culture, productivity and morale at FDA.

Beyond this, it is critical that FDA and sponsors communicate regularly throughout the development process so there are no "surprises" at the end. Additional bandwidth for meetings can help – especially for small companies. I believe FDA communication can and must be more specific to sponsors. It is not helpful to have to "read between the lines" to know that a program is not on track. Hiring additional FDA staff with small company experience to provide guidance would be helpful. Small companies are very fragile and significant change in timelines or additional unanticipated requirements late in the development cycle can destroy them – and worse deprive desperate patients of life saving alternatives.

The Honorable Jan Schakowsky

1. A recent NPR story discussed a gentleman who is very sick with Hepatitis C but who is unable to afford the new Hepatitis C treatment. According to the report, the new hepatitis C drug treatment costs about $100,000 per year. This is an example of a widespread disease where a treatment exists but cannot be accessed by all who need it. What can we do to develop a system where everyone can access and afford the new treatment and cures developed through investments in drug innovation?

   Answer: Thank you so much for this question. Pricing and affordability are certainly complex issues and I am not an expert in that area, but I will give my view. One of the greatest medical achievements of this century has been the curing of hepatitis C[7]. As a physician and scientist I must agree that innovation, even of this incredible magnitude and significance, that cannot be accessed is Pyrrhic victory. We must, therefore, work diligently to lower the cost of R&D, shorten the timelines and reduce uncertainty and failure. How can we do this? As I testified, we must invest in building an efficient infrastructure for clinical trials. Clinical trials working groups that are trained and ready to conduct studies on new products at every phase are needed. We should find ways to encourage and invest in creation of such networks. Industry itself is undertaking efforts to address issues of clinical trial cost and efficiency. Transcelerate Biomedical Inc.[89], a non-profit industry collaboration I helped found in 2012 is providing leadership in this area. The early results are very encouraging with more than 41,000 clinical investigators having been trained and a number of other promising initiatives underway - but much more needs to be done. More investment in surrogate markers and clinical endpoints is needed. The Biomarker Consortium[10] (managed by the Foundation for the NIH) is one such partnership that I have been involved with since its inception in 2006. It is a public-private biomedical research partnership managed by the Foundation for the National Institutes of Health that endeavors to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics. Founding members include the NIH, FDA, CMS, BIO, PhRMA and several pharmaceutical companies. A number of important studies have been conducted and are underway. We also need to continue to invest in FDA and public-private partnerships to support regulatory science including the Reagan-Udall Foundation[6]. Improving the capacity, training and culture of the FDA will also reduce uncertainty for both large and small companies to advance innovative products to accelerate and reduce the cost of innovation.

2. In your testimony, you stress the need to ensure that the FDA has the scientific workforce necessary to meet its regulatory mission that includes the ability to understand cutting edge technology and assess innovative products. You point out in your testimony that an important way to achieve this goal is to ensure adequate funding for FDA's intramural regulatory science programs. Would you discuss the importance of the regulatory science programs in enabling FDA to fulfill its mission of approving safe and effective drugs? Are there other ways that Congress can help ensure that FDA has the workforce to meet its needs?

   Answer: As I noted in my response to Rep. Bilirakis, I have interacted with FDA for more than 20 years. The large majority of FDA scientists are among the most dedicated civil servants one could

[7] Curing Chronic Hepatitis C — The Arc of a Medical Triumph. Raymond T. Chung, M.D., and Thomas F. Baumert, M.D. N Engl J Med 2014; 370:1576-1578
[8] Drug Makers Join Efforts in Research, Andrew Pollack, New York Times. Sep. 19, 2012
[9] http://www.transceleratebiopharmainc.com
[10] http://www.biomarkersconsortium.org

ever encounter. Among them are former academics and industry scientists who moved to FDA to help advance innovation and to improve the public health. Some are among the world's best clinical scientists – even though they may not always be recognized as such. A number of important contributions to the scientific literature are made by FDA scientists each year. These FDA scientists can make even more important contributions to original clinical and regulatory science if they are given the time and resources to pursue these activities. We must be cognizant that a number of the most senior and best scientists at FDA have or will soon retire. They will be difficult to replace.

PDUFA has certainly improved the productivity of the agency and provided more rigorous timelines for review. However this has come at a price in my view. FDA workload has outpaced their budget and staff. The intramural research program of FDA has been greatly reduced. FDA scientists have serious travel restrictions that do not allow them to attend scientific conferences as frequently as they should and to have meetings with leading academics. Thus the culture of the FDA has become increasingly "bureaucratized" and less scientific. One can contrast this culture with that of the NIH. Given the complexity of the new products in the pipeline including stem cell and gene therapy, smart devices and so on this does not bode for our competitive position in the world.

In my view, an increase in the budget for intramural science would attract higher quality scientists and raise their visibility in the academic community. The emphasis should be placed on clinical trials, regulatory science, toxicology, and other scientific disciplines directly related to the FDA mission. Increased budget for attendance at scientific conferences and training would also help. Top scientists should be recruited and retained. More interactions and cross appointments at NIH should be available. Academic rotations and even rotation of industry scientists to the FDA (with appropriate manage of conflict of interest) should be explored.

In addition to increasing resources, other reforms could also help. Excellent performers should be rewarded, with respect to both regulatory reviews but also scholarship and leadership. Poor performance should be managed. Nothing demoralizes an organization more than tolerance of under performance, increasing the burden on the productive staff. Information management technology needs to be upgraded. Processes need to be improved so that busy work is reduced in favor of value added activities. Peer review including more outside review of FDA science would be helpful as well. In my opinion, all of this would increase morale, productivity and greatly enhance the culture of the world's best regulatory agency – making it even better.

3. I have been a long-time advocate for increasing funding for the National Institutes of Health. Our investment in research saves lives and improves health. Adequately funding the NIH is also critical in helping to train our next generation of scientific leaders as well as supporting jobs in communities throughout this country. As you know, total inflation-adjusted funding for NIH peaked in fiscal year 2003, meaning that NIH had its largest purchasing power that year. As compared to 2003, inflation-adjusted funding is down 22.1% for fiscal year 2014. Would you explain what this dramatic reduction in purchasing power at the NIH means to the pace of drug innovation? How has this reduction affected our ability to develop our future scientific workforce and how does this harm our biomedical research capacity? Are there other ways that this reduction is affecting the pace of discovery of new cures and treatments?

   Thank you for your important testimony. Your testimony makes clear the harm caused by inadequately funding the NIH. I hope that we can work together to ensure that NIH has the resources it needs to ensure that we remain the world's leader in innovation and that we accelerate our ability to discover new treatments and cures that save lives and improve health.

Answer: The failure to at the very least maintain purchasing power at NIH puts the entire biomedical research enterprise at risk. NIH funding is critical to finding the next generation of cures AND in maintaining our competitiveness globally. In industry our success is largely based on the enormous body of scientific work produced by NIH funded research. There is an implicit partnership that has been extraordinarily complementary and effective. We simply cannot come close to replacing this amazing enterprise that has done so much for to advance the health of Americans and people around the world.

Training has always been an integral and critical component of the NIH mission. Fewer of the best and brightest minds are choosing an academic career because of the extreme difficulty they face in obtaining funding from NIH. Many established scientists are likewise leaving the bench in favor of other careers. I had the privilege of working on a Working Group commissioned by NIH Director, Dr. Francis Collins in 2011-2[11]. We found that 30% of biomedical PhD's pursue careers in the biotechnology and pharmaceutical industries. Thus one can expect a diminution in the pool of qualified scientists who will translate basic discoveries into new medicines. Some of these scientists can and will be replaced by foreign scientists and some research and development can and will also be moved abroad to take advantage of pools of talent, but in general this does not bode well for the health of the ecosystem or competitiveness of the US.

We are now on the threshold of the next generation of medicines – gene therapy, stem cell therapy and other interventions that could not have been dreamt of just a generation ago. We are also facing a crisis in health care that is largely the result of so many chronic and expensive illnesses. We are also facing many challenges to our global leadership in biomedical research and development that has contributed mightily to our prosperity and standing as a nation. We cannot and must not fail to continue to invest in NIH and FDA to ensure that we will find solutions to the diseases that are causing so much suffering in the US and abroad, maintain our competiveness and reduce the cost of health care for all Americans. I can think of no better use of our precious tax dollars and nothing that would ultimately create a higher return for our citizens.

[11] Biomedical Research Workforce Working Group, Draft Report National Institutes of Health, June 14, 2012 http://acd.od.nih.gov/bmw_report.pdf